Nivolumab (OPDIVO)
National Drug Monograph
March 2016
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Nivolumab is a monoclonal antibody that binds to the programmed-death 1 (PD-1) receptor on T-cells, blocking its interaction with its ligands PD-L1 and PD-L2 releasing PD-1 mediated pathway inhibition of the immune system resulting in anti-tumor responses. In combination with ipilimumab, another immune system checkpoint inhibitor, in melanoma results in greater T-cell function and better responses than either agent alone.

Indication(s) Under Review in this document (may include off label)	• Unresectable or metastatic melanoma:
	  ○ As a single agent for BRAF V600 wild-type unresectable or metastatic melanoma.
	  ○ As a single agent for BRAF mutation-positive unresectable or metastatic melanoma.
	  ○ In combination with ipilimumab in patients for patients with unresectable or metastatic melanoma.
	• Metastatic non-small cell lung cancer with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab.
	• Patients with advanced or metastatic renal cell carcinoma with a clear cell component who received prior anti-angiogenic therapy.

Dosage Form(s) Under Review	Dosage Form(s), Strength(s) Injection 40 mg/4 mL Injection 100mg/10 mL
REMS	☐ REMS ☒ No REMS ☐ Postmarketing Requirements *See Other Considerations for additional REMS information*
Pregnancy	Based on its mechanism of action and data form animal studies, nivolumab can cause fetal harm when administered to a pregnant woman. *See Special Populations for additional information*

Executive Summary

Efficacy	• In metastatic melanoma in previously treated patients, higher objective response rates and durable response versus chemotherapy. In treatment naïve patients, single agent nivolumab superior to dacarbazine for overall survival in BRAF wild-type. In treatment naïve BRAF mutated, nivolumab and nivolumab/ipilimumab superior to ipilimumab for progression free survival. Note that in a subgroup analysis of BRAF mutated tumors, the HR for PFS crossed 1 for the analysis of nivolumab versus ipilimumab. • In non-small cell lung cancer in previously treated patients, nivolumab superior to docetaxel for overall survival in both non-squamous and squamous disease. • In renal cell cancer after 1-2 prior antiangiogenic therapies, nivolumab was

	superior to everolimus for overall survival.
Safety	• Immune-related toxicities are rare but potentially serious. Early recognition and prompt treatment are key to resolution. • Common adverse events: Melanoma (≥20%): rash (single agent); rash, pruritus, headache, vomiting, colitis (in combination with ipilimumab) NSCLC (≥20%): fatigue, musculoskeletal pain, decreased appetite, cough, Constipation • While the overall percentage of patients with a grade 3 or 4 adverse event is over 20% in most clinical trials, the incidence of each grade 3 or 4 events is small. • Discontinuation rates for adverse events was generally less than in the comparator arm.
Other Considerations	

Outcome in clinically significant area	Melanoma Previously Treated (vs chemo): ORR 31.7%; PFS 4.7 mos; OS not available Melanoma Treatment naïve (vs dacarbazine): OS NR vs 10.8 mos; PFS 5.1 vs 2.2 mos Melanoma Treatment naïve + ipilimumab: PFS 11.5 vs 6.9 mos (NI vs N); OS not available NSCLC (nonsquamous)(vs docetaxel): OS 12.2 vs 9.4 mos NSCLC (squamous)(vs docetaxel): OS 9.2 vs 6.0 Renal Cell (vs everolimus): OS 25 vs 19.6 mos
Effect Size	Melanoma Previously Treated: PFS HR 0.82 (99%CI 0.32-2.05) Melanoma Treatment naïve: OS HR 0.42 (99%CI 0.25-0.73); PFS HR 0.43 Melanoma Treatment naïve + ipilimumab: PFS (NI vs I) HR 0.42; (N vs I) HR 0.57 (NI vs N) HR 0.74 (99.5%CI 0.60-0.92) NSCLC (nonsquamous): OS HR 0.73 (95%CI 0.59-0.89) NSCLC (squamous): OS HR 0.59 (95%CI 0.44-0.79) Renal Cell: OS HR 0.73 (98.5%CI 0.57-0.93)
Potential Harms	Single agent melanoma: Grade 3 or 4 in 42% Combination with ipilimumab in melanoma: Grade 3 or 4 in 69% NSCLC nonsquamous: Grade 3 or 4 in 47% NSCLC squamous: Grade 3 or 4 in 7% Renal Cell: Grade 3 or 4 in 19%
Net Clinical Benefit	Melanoma Previously Treated: Negative Melanoma Treatment Naïve: Moderate Melanoma Treatment naïve + ipilimumab: Moderate NSCLC (nonsquamous): Moderate NSCLC (squamous): Substantial Renal Cell: Substantial

Projected Place in Therapy	• As this is an evolving class of drugs, place in therapy should be limited to FDA indications.

Background

Purpose for review

The purposes of this monograph are to (1) evaluate evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating nivolumab for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational uses in the VA.

Issues to be determined:

- Evidence of need?
- Does nivolumab offer advantages to currently available alternatives?
- Does nivolumab offer advantages over current VANF agents?

- What safety issues need to be considered?
- Does nivolumab have specific characteristics best managed by the non-formulary process, prior authorization, criteria for use?

Other therapeutic options

Unresectable or metastatic melanoma

Formulary Alternatives	Other Considerations
Cisplatin	If not used 1st line and not the same class as 1st line (with vinblastine, dacarbazine, IL-2 and interferon; high incidence of toxicity).
Carboplatin	If not used 1st line and not the same class as 1st line
Vinblastine	If not used 1st line and not the same class as 1st line (see cisplatin)
Carmustine	If not used 1st line and not the same class as 1st line
Imatinib	If c-KIT mutation positive
Paclitaxel	If not used 1st line and not the same class as 1st line
Dacarbazine	If not used 1st line and not the same class as 1st line (see cisplatin)
Carboplatin/paclitaxel	If not used 1st line and not the same class as 1st line
Non-formulary Alternative (if applicable)	**Other Considerations**
Pembrolizumab	PD-L1 blocker; 1st line or 2nd line
Ipilimumab	Single agent or in combination with nivolumab
Dabrafenib	BRAF mutation positive; 1st line or 2nd line if not used in 1st line; single agent or in combination with trametinib (preferred)
Vemurafenib	BRAF mutation positive; 1st line or 2nd line if not used in 1st line
Temozolomide	
High-dose Interleukin-2`	Limited to good PS and centers experienced with administering in ICU
Nab-paclitaxel	Protein-bound paclitaxel

Non-small cell lung cancer after progression on platinum therapy

Formulary Alternatives	Other Considerations
Erlotinib	With or without EGFR mutation; indirect comparison better OS with nivolumab after chemotherapy
Gemcitabine infusion	PS 0-2
Docetaxel	PS 0-2
Non-formulary Alternative (if applicable)	**Other Considerations**
Pembrolizumab	PD-L1 blocker; approved only for tumors expressing PD-L1
Pemetrexed	Non-squamous histology
Ramucirumab	With docetaxel

Unresectable or Metastatic Renal Cell Carcinoma after antiangiogenic therapy

Formulary Alternatives	Other Considerations
Bevacizumab	Phase II data for use after cytokine therapy; limited data on use after TKI therapy

Non-formulary Alternative (if applicable)	Other Considerations
Everolimus	OS better with nivolumab
Axitinib	Better PFS vs sorafenib but no difference in OS (but high crossover rate)
Sorafenib	Best after cytokine therapy; may be used after TKI therapy
Sunitinib	Best after cytokine therapy but preferred 1st line agent; retrospective analyses of sequencing with sorafenib
Pazopanib	Best after cytokine therapy; more limited data after prior TKI therapy
Temsirolimus	Phase II data after cytokine therapy. In phase 3 data after sunitinib, when compared to sorafenib no difference in PFS and sorafenib had better OS; in a subgroup of patients with a short response to 1st line sunitinib, temsirolimus had better OS vs sorafenib

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (1966 to October 2015) using the search term nivolumab. The search was limited to the Pub Med Clinical Queries Filter for Therapy (specific/narrow and sensitive/broad) and studies performed in humans and published in the English language. Reference lists of review articles and evidence based databases and treatment guidelines were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Review of Efficacy

Table 1. Unresectable or metastatic melanoma

Study	Setting	Pts	ECOG PS	Treatment	Response (%)	PFS months	OS months
Previously treated							
CheckMate 037[1] Bristol-Myers Squibb and senior investigators	Unresectable or metastatic If BRAF WT progression after ipilimumab If BRAF V600 mutation positive progression on ipilimumab and BRAF inhibitor	N=631 N=272 nivolumab N=133 investigators choice of chemo Age: 59 Male: 65% ECOG 0: 60% PD-L1 pos: 49% BRAF mut: 22%	0-1	Nivolumab 3mg/kg IV every 2 weeks Chemo: either Dacarbazine 1000mg/m2 IV every 3 weeks or carboplatin AUC=6 plus paclitaxel 185mg/m2 IV every 3 weeks	Primary Confirmed objective response per-protocol: Nivolumab:31.7% Chemo: 10.6% Response per intention to treat: Nivolumab: 31.1% Chemo: 8.3% Med duration of response: not yet reached vs 3.5 months	ITT population 4.7 vs 4.2 HR 0.82 (99%CI 0.32-2.05) 6 mos PFS: 48% vs 34%	N/A
Treatment naive							
CheckMate 066[2] Bristol-Myers Squibb	Unresectable or metastatic Without *BRAF* mutation And availability of	N=418 N=210 nivolumab N=208 dacarbazine Age: 64	0-1	Nivolumab 3 mg/kg IV every 2 weeks plus placebo every 3 wks Dacarbazine 1000	Objective response rate nivolumab 40% vs dacarbazine 13.9% Odds ratio 4.06	5.1 vs 2.2 mos HR 0.43 (95%CI 0.34-0.56; P<0.001)	Primary NR vs 10.8 mos HR 0.42 (99.79%CI

	tissue for PD-L1 biomarker analysis	Male: 57.6% ECOG 0: 70.5% PD-L1 pos: 35.2%		mg/m^2 IV every 3 weeks plus placebo every 2 wks Until progression (treatment after progression permitted if clinical benefit seen and no substantial adverse effects)	Complete response Nivolumab: 7.6% Dacarbazine: 1% Med duration of response Nivolumab=NR Dacarbazine=6 mos		0.25-0.73; P<0.001) OS 1 yr: 72.9 vs 42.1% PD-L1 pos:HR 0.30 (unadjusted) PD-L1 neg: HR 0.48
CheckMate 069[3] Bristol-Myers Squibb	Unresectable or metastatic treatment naïve with measurable disease Availability of tissue for PD-L1 biomarker analysis Randomized phase 2	N=142 N=95 nivolumab + ipilimumab N=47 ipilimumab Age: 64 Male 66% ECOG 0: 83% BRAF mut: 24%	0-1	Nivolumab 1 mg/kg IV every 3 weeks X 4 doses plus ipilimumab 3 mg/kg IV every 3 weeks X 4 doses Then maintenance nivolumab 3mg/kg IV every 2 weeks Same dose schedule with nivolumab placebo in both the combination and maintenance phase	Primary BRAF wild type Objective response rate: 61% vs 11% Odds ratio 12.96 Obj response independent of PD-L1 status Complete response: 22% vs 0% Med duration of response: NR either group BRAF mutation Obj Response: 52% combination group Complete response: 22% combination grp	BRAF wild type NR vs 4.4 mos HR 0.40 (95% CI 0.23-0.68) BRAF mutation 8.5 vs 2.7 mos HR 0.38 (95%CI 0.15-1.00)	N/A
CheckMate 067[4] Bristol-Myers Squibb	Unresectable or metastatic No prior treatment Measurable disease Tissue available for PD-L1 biomarker analysis Known BRAF mutation status	N=945 N=316 nivolumab N=314 combination N=315 ipilimumab Age:60 Male: 65% ECOG 0: 73% PD-L1 pos: 23.6% BRAF mut: 31.5%	0-1	Nivolumab 3 mg/kg IV every 2 weeks (plus ipi placebo) Nivolumab 1 mg/kg IV every 3 weeks plus ipilimumab 3 mg/kg IV every 3 weeks X 4 doses; then maintenance nivolumab 3 mg/kg IV every 2 weeks Ipilimumab 3 mg/kg IV every 3 weeks (plus nivolumab placebo)	Objective response rate: Nivo: 43.7% Combo: 57.6% Ipi: 19% Complete response: Nivo: 8.9% Combo: 11.5% Ipi: 2.2% Obj Response Rates PD-L1 positive: Nivo: 57.5% Combo: 72.1% Ipi: 21.3% PD-L1 negative: Nivo: 41.3% Combo: 54.8% Ipi: 17.8%	Co-primary Nivo: 6.9 mos Combo: 11.5 mos Ipi: 2.9 mos Combo vs ipi: HR 0.42 (99.5%CI 0.31-0.57; P<0.001) Nivo vs ipi: HR 0.57 (99.5%CI 0.43-0.76; P<0.001) Combo vs Nivo: HR 0.74 (95%CI 0.60-0.92) PD-L1 positive: Nivo: 14mos Combo: 14 mos Ipi: 3.9 mos PD-L1 negative:	Co-primary Results not yet available

							Nivo: 5.3 mos Combo: 11.2 mos Ipi: 2.8 mos

WT=wild type; ECOG=Eastern Cooperative Oncology Group; PS=Performance Status; PD-L1=Programmed Death Ligand 1; PFS=Progression Free Survival; ITT=intention to treat; NR=not reached; HR=hazard ratio; OS=overall survival

- In patients with metastatic melanoma that was previously treated, including patients with BRAF wild type and V600 mutations, nivolumab produced higher overall response rates versus investigator's choice of chemotherapy.
- The responses in the nivolumab arm were durable as the median duration of response has not been reached versus a duration of response of 3.6 months for chemotherapy. This pattern of durable responses is similar to other immunotherapies. The results of the overall survival analysis are not yet available.
- In treatment naïve patients with unresectable or metastatic melanoma without BRAF mutation, nivolumab was superior versus dacarbazine in overall survival with a median overall survival not yet reached versus 10.8 months with dacarbazine. The survival advantage was irrespective of PD-L1 expression.
- In treatment naïve patients with unresectable or metastatic melanoma with a BRAF mutation, PFS was improved in patients receiving nivolumab or nivolumab plus ipilimumab versus ipilimumab itself. The PFS in the combination arm was also improved compared to nivolumab. PFS in patients whose tumors express PD-L1 was the same in the combination or nivolumab arm and was better than the ipilimumab arm. PFS was better in the combination arm versus nivolumab or ipilimumab in patients whose tumors did not express PD-L1. The results of the co-primary outcome of overall survival are not yet available.
- Note that in a subgroup analysis of BRAF mutated tumors, the HR for PFS crossed 1 for the analysis of nivolumab versus ipilimumab.

Table 2. Non-small cell lung cancer

Study	Setting	Pts	ECOG PS	Treatment	Response (%)	PFS months	OS months
Nonsquamous							
CheckMate 057[5] Bristol-Myers Squibb	Stage IIIB or IV or recurrent after radiation or surgery And Recurrence or progressed on 1 prior platinum based doublet If EGFR mutation pos or ALK translocation allowed additional line of TKI therapy. Maintenance therapy allowed (continuation or switch therapy)	N=582 N=292 Nivolumab N=290 Docetaxel Med age: 61 Male: 52% White: 91% ECOG 1: 71% EGFR mut: 15% ALK: 4% 1 prior tx: 88%	0-1	Nivolumab 3 mg/kg IV every 2 weeks Docetaxel 75 mg/m^2 IV every 3 weeks Until progression or discontinuation	Objective response rate: 19 vs 12% Med duration of response: 17.2 vs 5.6 mos	2.3 vs 4.2 HR 0.92 (95%CI0.77-1.1; P=0.39) PFS 1 yr: 8% vs 19% N=71 nivolumab patients continued therapy beyond initial progression; 23% had a nonconventional pattern of benefit	Primary Interim: 12.2 vs 9.4 HR 0.73 (95%CI 0.59-0.89; P=0.002) OS 1 yr: 51% vs 39% Updated 12.2 vs 9.4 HR 0.72 (95%CI 0.60-0.88;P<0.001) OS 18 mos: 39% vs 23% Nivolumab associated with higher objective response, longer PFS and OS at all pre-specified PD-L1 expression levels (1%, 5%, 10%)
Squamous							
CheckMate	Stage IIIB or IV	N=272	0-1	Nivolumab 3	Objective	3.5 vs 2.8	Primary

017[6] Bristol-Myers Squibb	squamous cell NSCLC with disease recurrence after 1 prior platinum containing regimen Tissue for biomarkers Stable brain mets allowed Excluded: autoimmune disease, symptomatic interstitial lung disease, systemic immunosuppression, prior docetaxel Prior maintenance therapy (e.g. EGFR TKI, etc.) allowed	N=135 Nivolumab N=137 Docetaxel Age: 62 Male:82% White: 90% Stage IV: 78% ECOG 1: 79%	mg/kg IV every 2 weeks Docetaxel 75 mg/m^2 IV every 3 weeks Until progression or discontinuation	response: 20% vs 9% Med duration: Not reached vs 8.4 mos	HR 0.62 (95%CI 0.47-0.81; P<0.001) PFS 1 yr: 21% vs 6%	9.2 vs 6.0 HR 0.59 (95%CI 0.44-0.79; P<0.001) OS 1yr: 42 vs 24% PD-L1 expression was not prognostic or predictive of any efficacy endpoint

EGFR=epidermal growth factor receptor; ALK=anaplastic lymphoma kinase; ECOG=Eastern Cooperative Oncology Group; PS=Performance Status; PD-L1=Programmed Death Ligand 1; PFS=Progression Free Survival; HR=hazard ratio; OS=overall survival

- In patients with previously treated non-squamous non-small cell lung cancer, nivolumab increased overall survival compared to standard docetaxel therapy.
- The overall survival advantage was seen at 12 months and 18 months.
- Objective response, improved PFS and improved overall survival were not associated with PD-L1 expression.
- In patients with previously treated squamous non-small cell lung cancer, nivolumab increased overall survival compared to standard docetaxel therapy.
- The overall survival advantage was also seen at the 12 month mark.
- The median duration of response has not yet been reached.
- Objective response, improved PFS and improved overall survival were not associated with PD-L1 expression.
- Subjects who received adjuvant or neoadjuvant platinum-doublet chemotherapy (after surgery and/or radiation therapy) and developed recurrent or metastatic disease within 6 months of completing therapy were eligible. However, patients with recurrent disease > 6 months after adjuvant or neoadjuvant platinum based chemotherapy also needed to subsequently progress during or after a platinum doublet regimen given to treat the recurrence to be eligible for nivolumab.

Table 3. Renal Cell Carcinoma

Study	**Setting**	**Pts**	**ECOG PS**	**Treatment**	**Response (%)**	**PFS months**	**OS months**
CheckMate 025[7] Bristol-Myers Squibb	Advanced or metastatic renal-cell carcinoma with a clear cell component 1-2 previous antiangiogenic therapies	N=821 N=406 Nivolumab N=397 Everolimus Age: 62 Male: 77% White: 86% MSKCC risk group Favorable: 35% Intermediate: 49% Poor: 16% 1 prev therapy: 72%	KPS at least 70	Nivolumab 3mg/kg IV every 2 weeks Everolimus 10 mg orally daily	Objective response rate: 25 vs 5% Odds ratio 5.98 Complete response: 1% vs <1% Duration of response: 12 vs 12 mos	4.6 vs 4.4 HR 0.88 (95%CI 0.75-1.03; P=0.11)	Primary 25 vs 19.6 HR 0.73 (98.5%CI 0.57-0.93; P=0.002)

MSKCC=Memorial Sloan Kettering Cancer Center; KPS=Karnofsky Performance Status; PD-L1=Programmed Death Ligand 1; PFS=Progression Free Survival; HR=hazard ratio; OS=overall survival

- In patients with advanced or metastatic renal cell carcinoma with a clear cell component who progressed on 1-2 prior antiangiogenic therapies, nivolumab increased overall survival versus the mTOR inhibitor everolimus. The point

estimate for overall survival favored nivolumab in multiple subgroups, but the confidence intervals crossed 1 for the following groups: favorable MSKCC score, 2 previous antiangiogenic regimens, patients in western Europe and rest of the world, Age <65 years old, and female sex.

- Quality of life scores, Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease-Related Symptoms (FKSI-DRS), in the nivolumab group increased (improved) over time (weeks 32-104) and differed significantly from the scores in the everolimus treated patients which decreased (worsened) over time.
- There was a numerical overall survival advantage for nivolumab irrespective of PD-L1 expression, however for those with PD-L1 1% or greater the 95% confidence interval crossed 1 which did not occur in those with PD-L1 <1%.

Potential Off-Label Use

- Ovarian carcinoma[8]
- Relapsed/refractory Hodgkin's Lymphoma (CheckMate 039)[9]
- Glioblastoma Multiforme
- Hepatocellular Carcinoma
- Bladder/urothelial ancer
- Head and Neck Cancer
- Colorectal carcinoma
- Gastric cancer
- Triple negative breast cancer
- Non-Hodgkin's lymphoma
- Esophageal cancer
- Adjuvant melanoma
- Nivolumab + chemo in NSCLC
- Nivolumab + ipilimumab in Renal Cell Cancer
- Nivolumab + ipilimumab in NSCLC

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	• None
Contraindications	• None

Warnings/Precautions	• Immune-mediated colitis: withhold for moderate or severe and permanently discontinue if life-threatening
	• Immune-mediated hepatitis: withhold for moderate and permanently discontinue for severe or life-threatening (transaminases or total bilirubin)
	• Immune-mediated endocrinopathies:
	  ○ Hypophysitis: withhold for moderate or severe and permanently discontinue if life-threatening
	  ○ Adrenal insufficiency: withhold for moderate and permanently discontinue for severe or life-threatening
	  ○ Thyroid: monitor for changes and initiate hormone replacement if needed
	• Immune-mediated nephritis and renal dysfunction: withhold for moderate or severe and permanently discontinue for life-threatening elevation in serum creatinine.
	• Immune-mediated rash: withhold for severe and permanently discontinue for life-threatening
	• Immune-mediated encephalitis: withhold for new-onset moderate or severe neurologic signs or symptoms and permanently discontinue for immune-mediated encephalitis
	• Embryofetal toxicity: can cause fetal harm. Advise of potential risk to fetus and use effective contraception

Safety Considerations

- Immune-mediated reactions are the most significant safety concerns for this drug. Like with other immune-

modulators, early recognition and initiation of treatment are key.

Adverse Reactions

Common adverse reactions	Melanoma (≥20%): rash (single agent); rash, pruritus, headache, vomiting, colitis (in combination with ipilimumab) NSCLC (≥20%): fatigue, musculoskeletal pain, decrease appetite, cough, constipation Renal cell (≥20%): asthenic conditions, cough, nausea, rash, dyspnea, diarrhea, constipation, decreased appetite, back pain, arthralgia
Death/Serious adverse reactions	Melanoma (2% - <5%): abdominal pain, hyponatremia, increased aspartate aminotransferase, increased lipase. (≥10%): rash Melanoma in combination with ipilimumab: colitis, diarrhea not treated with steroids, increased ALT, pneumonitis, AST increase, pyrexia; in at least 20%: rash, pruritus, headache, vomiting, colitis. NSCLC (at least 2%): pneumonia, pulmonary embolism, death due to limbic encephalitis Renal cell (at least 2%): acute kidney injury, pleural effusion, pneumonia, diarrhea, hypercalcemia
Discontinuations due to adverse reactions	Melanoma (single): 6.8 vs 11.7% Melanoma (combination):52.1% vs 24.3% (ipi); 36.4% vs 14.8% (ipi) vs 7.7% (nivolumab) NSCLC:3-5% vs 10-15% (docetaxel) Renal cell: 16% vs 19% (everolimus)

Drug Interactions

Drug-Drug Interactions

- No pharmacokinetic drug-drug interaction studies

Risk Evaluation

As of October 1, 2015

	Comments
Sentinel event advisories	• None • Sources: ISMP, FDA, TJC
Look-alike/sound-alike error potentials	See table below • Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Nivolumab 40mg/4mL, 100mg/10mL vial	None	None	None	Nebivolol Nimodipine Natalizumab
Opdivo	None	None	None	Ovide Optiray Forfivo

Other Considerations

Outcome in clinically significant area	Melanoma Previously Treated (vs chemo): ORR 31.7%; PFS 4.7 mos; OS not available Melanoma Treatment naïve (vs dacarbazine): OS NR vs 10.8 mos; PFS 5.1 vs 2.2 mos

	Melanoma Treatment naïve + ipilimumab: PFS 11.5 vs 6.9 mos (NI vs N); OS not available NSCLC (nonsquamous)(vs docetaxel): OS 12.2 vs 9.4 mos NSCLC (squamous) (vs docetaxel): OS 9.2 vs 6.0 Renal Cell (vs everolimus): OS 25 vs 19.6 mos
Effect Size	Melanoma Previously Treated: PFS HR 0.82 (99%CI 0.32-2.05) Melanoma Treatment naïve: OS HR 0.42 (99%CI 0.25-0.73); PFS HR 0.43 Melanoma Treatment naïve + ipilimumab: PFS (NI vs I) HR 0.42; (N vs I) HR 0.57 (NI vs N) HR 0.74 (99.5%CI 0.60-0.92) NSCLC (nonsquamous): OS HR 0.73 (95%CI 0.59-0.89) NSCLC (squamous): OS HR 0.59 (95%CI 0.44-0.79) Renal Cell: OS HR 0.73 (98.5%CI 0.57-0.93)
Potential Harms	Single agent melanoma: Grade 3 or 4 in 42% Combination with ipilimumab in melanoma: Grade 3 or 4 in 69% NSCLC nonsquamous: Grade 3 or 4 in 47% NSCLC squamous: Grade 3 or 4 in 7% Renal Cell: Grade 3 or 4 in 19%
Net Clinical Benefit	Melanoma Previously Treated: Negative Melanoma Treatment Naïve: Moderate Melanoma Treatment naïve + ipilimumab: Moderate NSCLC (nonsquamous): Moderate NSCLC (squamous): Substantial Renal Cell: Substantial

Definitions

Outcome in clinically significant area: morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life

Effect Size: odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio

Potential Harms: Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)

Net Clinical Benefit: Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

Dosing and Administration

- Refer to the package insert for full dosing information and recommended dose modifications
- Melanoma (single agent): Nivolumab 3mg/kg as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.
- Melanoma in combination with ipilimumab: Nivolumab 1mg/kg as an intravenous infusion over 60 minutes, followed by ipilimumab on the same day, every 3 weeks for 4 doses. Subsequent doses of nivolumab is 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity.
- NSCLC: Nivolumab 3mg/kg as an intravenous infusion over 60 minutes every 2 weeks.
- Renal cell carcinoma (clear cell): Nivolumab 3 mg/kg as an intravenous infusion over 60 minutes every 2 weeks.

Special Populations (Adults)

	Comments
Elderly	• No differences in safety or efficacy in 2nd line single-agent trial in melanoma (35% >65 yrs old and 15% ≥75 yrs old)or 2nd[t] line single agent trial in non-squamous NSCLC (37% >65 yrs old and 7% ≥75 yrs old). In combination with ipilimumab, too few patients >65 yrs old to evaluate for efficacy and safety.
Pregnancy	• Risk summary: Based on mechanism of action and animal data, nivolumab can cause fetal harm when given to a pregnant female. In animals given nivolumab from onset of organogenesis through delivery there was an increased incidence of abortion and premature infant death. Nivolumab is an immunoglobulin G4 and human IbG4 is known to cross placenta and can be transmitted from mother to fetus. There is no available human data.
Lactation	• Risk Summary: It is not known if nivolumab is present in breast milk. Because drugs, including antibodies are excreted in breast milk and due to the potential serious adverse reactions in nursing infants from nivolumab, women should be advised to stop breastfeeding during therapy with nivolumab.
Females and Males of Reproductive	• Advise females of reproductive potential to use effective

Potential		contraception during nivolumab therapy and for at least 5 months following the last dose of nivolumab.
Renal Impairment	•	Based on population pharmacokinetics, no dose adjustment is recommended in patients with renal impairment.
Hepatic Impairment	•	Based on population pharmacokinetics, no dose adjustment is recommended for mild hepatic impairment. Nivolumab has not been studied in patients with moderate or severe hepatic impairment.
Pharmacogenetics/genomics	•	No data identified

Projected Place in Therapy

- Metastatic melanoma: Current FDA approved choices for therapy for metastatic melanoma that is refractory to ipilimumab and/or BRAF inhibition if BRAF V600 mutation positive, include dacarbazine and interleukin-2, both providing limited benefit and considerable toxicity. For front-line therapy, FDA approved drugs include dacarbazine, interleukin-2, interferon, ipilimumab, pembrolizumab and TKIs for tumors with actionable mutations: vemurafenib, dabrafenib, trametinib, and cobimetinib.
- Lung cancer is one of the top 2 cancers in the VA.
- In non-squamous non-small cell lung cancer that has progressed on a platinum based chemotherapy regimen, there are a number of drugs available for use in this setting. Subsequent therapy in the context of platinum failure does not depend on the tumor molecular profile.
- In squamous non-small cell lung cancer that has progressed on 1 prior platinum based chemotherapy, choices for subsequent therapy are more limited.
- In patients with renal cell carcinoma with a clear cell component, therapy following antiangiogenic therapy is everolimus, an mTOR inhibitor.
- The overall quality of the evidence for nivolumab is high. Some caveats including the lack of availability of overall survival data for previously treated patients with melanoma and in treatment naïve patients with melanoma and a BRAF mutation until sometime in 2016. The quality of data in non-small cell lung cancer is also high, but there is some question about choosing the right patients especially in the non-squamous setting. In renal cell with clear cell component, there are more limited choices with good data for 2nd or 3rd line therapy after antiangiogenic therapy. The quality of data with nivolumab is high and an FDA indication in this setting is expected shortly.
- On ongoing question in this class is choosing the best patients for therapy. Although PD-L1 expression has been tested in clinical trials there is no validation of the staining method and therefore no standardized method for measurement. There is also no standard interpretation of the correct cut-point for declaring PD-L1 expression positivity: in clinical trials in this class of drugs 1%, 5%, 10% and 50% have all been utilized. There are other biomarkers that may become important in the future with predicting which patients are more likely to respond (e.g. tumor-infiltrating lymphocytes and DNA mismatch-repair deficiency).
- Place in therapy should generally follow the current FDA indications until we have more detailed information on using biomarkers to delineate subpopulations to treat or not treat.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.

Appendix B: Approval Endpoints (use for oncology NMEs)

Table 1. A Comparison of Important Cancer Approval Endpoints

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	• Randomized studies essential • Blinding not essential	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes noncancer deaths
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	• Randomized blinded studies	• Patient perspective of direct clinical benefit	• Blinding is often difficult • Data are frequently missing or incomplete • Clinical significance of small changes is unknown • Multiple analyses • Lack of validated instruments
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Objective Response Rate	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Assessed earlier and in smaller studies compared with survival studies • Effect attributable to drug, not natural history	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Only a subset of patients with benefit
Complete Response	Surrogate for accelerated approval or regular approval*	• Single-arm or randomized studies can be used • Blinding preferred in comparative studies • Blinded review recommended	• Can be assessed in single-arm studies • Durable complete responses can represent clinical benefit • Assessed earlier and in smaller studies compared with survival studies	• Not a direct measure of benefit in all cases • Not a comprehensive measure of drug activity • Small subset of patients with benefit
Progression- Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	• Randomized studies essential • Blinding preferred • Blinded review recommended	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies • Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.